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Genetics in congenital anomalies of the hand

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Abstract

Congenital anomalies of the hand are malformations occurring during the development of the human limb, and present as isolated disorders or as a part of a syndrome. During the last years, molecular analysis techniques have offered increasing knowledge about the molecular basis of hand malformations. Disturbances in the signalling pathways during the development of the upper limb result in malformations of upper extremity. At present, several genes have been identified as responsible for hand anomalies and other have been recognized as suspect genes related to them. Different and new high throughput methods have been introduced for the identification of the gene mutations. In the current editorial, we summarize concisely the current molecular status of isolated hand genetic disorders and the recent progress in molecular genetics, including the genes related to the disorder. This progress improves the knowledge of these disorders and has implications on genetic counselling and prenatal diagnosis.

Key Words: Hand; Gene; Mutation; Molecular; Diagnosis; Disorders

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Core Tip: The genetic basis of hand disorders is elucidated by the expansion of knowledge and introduction of molecular analysis techniques which contribute to the identification of new genes responsible for them. New genes and mutations are being isolated and correlated with the disorder based on the advances in sequencing technology, such as next generation sequencing (NGS) and genetic consultation and future therapeutic developments are enhanced. There appears to be a gap in the literature concerning the knowledge about the genetic basis of all hand disorders. The current molecular status of them is discussed and a summary of different genes, already identified or suspected to be related with them is presented.

INTRODUCTION

Congenital anomalies of the hand very often have an autosomal dominant pattern of inheritance and most of them have o monogenic genetic basis with variable penetrance[1]. They are related with a disturbance of the normal procedure of the development of limb, with diverse aetiology and variable clinical features[2], and their proposed classification system has changed throughout the years, incorporating a rather molecular than anatomic scope of the phenotypes. Initially, the Swanson Classification of congenital anomalies of the hand, including nine categories of malformations, was used by the International Federation of Societies for Surgery of the Hand (IFSSH) Committee on Congenital Conditions, as it was considered effective according to the knowledge at the time. Later on, as the awareness of pathogenetic routes and molecular basis of limb formation expanded, the OMT classification was presented, dividing hand anomalies into four groups: Malformations (which include the majority of the disorders), deformations, dysplasias and syndromes[3].

To date, several loci and disease-causing genes, including all four categories of hand disorders have been identified in humans, and correlated to specific phenotypes.

Since these phenotype manifestations are indicators that the fetus or the newborn may suffer from a syndrome, the ability to identify the potential syndromes associated with these anomalies, are important for the clinician. Additionally, it is important to distinguish between syndromic and non-syndromic cases for reasons of genetic counselling. Therefore we present a concise summary of the main genes that are responsible for the disorders, whose etiology is mainly based on known genetic and not external factors, and lead to hand disorder phenotypes when mutated.

POLYDACTYLY

Preaxial/ Radial polydactyly

Preaxial polydactyly is a malformation described by extra digit on the radial side of hand with incidence as high as 1 in 3000 births. It follows an autosomal dominant

inheritance model with reduced penetrance[4]. Thumb polydactyly has been further subdivided into six subtypes by Wassel according to the level of (metacarpal, proximal or distal phalange) and the extent of duplication (partial, complete)[5,6].NGS analysis in a patient with Wassel III polydactyly identified 3 gene mutations as following: (a)substitution c.1639 G>T in *RPGRIP1* gene, (b) insertion of adenine in *TMEM216* gene, and (c) A>G nucleotide substitution (c.490) in *FBN1* gene. In a patient with Wassel IV duplication, the following mutations were identified: a) adenine duplicated in exon 45 of *CEP290* gene, b) two substitutions in *RPGRIP1* gene, c.1639 G>T and c.685 G>A, (c) adenine insertion in *TMEM216* gene, c.432-11 432-10 insA, (d) substitution G>C c.8249 in *MEGF8* gene and e) substitution T>A c.548 in *CEP164* gene. Thesemutations are suspected to be involved in the formation of thumb duplication phenotype[7] . Another suspected way of development of preaxial polydactyly is the overexpression of *HES1* gene. The produced protein is considered to intervene in SHH/GLI signaling axis and results to the manifestation of preaxial polydactyly[8]. The disease gene locus with triphalangeal thumb was identified in chromosome 7q36[9].Point mutations (105C>G, 305A>T, 323T>C, 404G>A, 295T>C, 4909 C>T, 297G>A, 334T>G, 402C>Tand 545G>A) have been identified[10], a 739A>G transition near the 5- end of the zone of polarizing activity regulatory sequence(*ZRS*) and a 621C>G mutation in the *ZRS* of the *LMBR1* gene have also been mapped[11]. Two more novel mutations (ZRS131A > T and ZRS474C > G) correlated with preaxial polydactyly were identified in a recent study of a Chinese family[12]. No mutations have been identified for index finger polydactyly, which is inherited with an autosomal dominant trait[13].

Postaxial polydactyly

Postaxial polydactyly presents with extra digits on the ulnar side of the hands. Mutations in genes *ZNF141, GLI3, IQCE, GLI1, FAM92A1, KIAA0825,* and *DACH1* have been isolated and their involvement in this manifestation is identified[14].

Responsible gene locus have been mapped to 7pl5-q11.23, 13q21-q32 [15] , 19p13.2-p13.1, 7q21-q34 and 13q13.3-13q21.2 regions using genome-wide scan. Subsequently, two heterozygous mutations, p.A765PfsX14 and p.R539TfsX12 in *GLI3* gene[16,17] and P.T474I mutation in the *ZNF141* gene have been identified using exome sequencing[18]. Recently, a new suspected mutation in *GLI1* gene (c.1133C > T) was isolated in an Indian family with the disorder[19] and a mutation in *KIAA0825* gene has been isolated and suspected, although this gene's encoded protein's role in limb formation is still unclear[20].

Central polydactyly and complex types of polydactyly

Central polydactyly phenotype is characterized by duplication of the 2nd,3rd, or 4th digits[21]. No diseasecausing locus or gene responsible for central polydactyly has been identified. Mirror image polydactyly is characterised by mirror-image duplication of fingers and toes [22]A mutation at 14q13 of the *MIPOL1*gene and two heterozygous deletions including the *PITX1* gene were identified [23].

SPLIT-HAND MALFORMATION

Split-hand malformation may occur as an isolated trait or accompanied with other defects. It manifests as a clinically heterogeneous disorder characterized by absent central digital rays, which result to median clefts of the hand. Responsible mutations map to chromosome 7q21.3-q22.1, chromosome Xq26 and chromosome 10q25[24]. *LBX1, BTRC, POLL, FBXW4, BTRC* gene mutations are reported as responsible for the disease[25]. Recent molecular studies have expanded the list of suspected gene mutations. A *TP63* gene translocation, *FGFR1, BHLHA9, LRP6, UBA2* and *WNT10B* gene mutations have been recently identified[26-30].

RADIAL RAY DEFECTS

They occur as an isolated malformation or syndromic. They are characterized by partial or complete absence of radial ray structures. Radial defects comprise a large group of diseases. They are associatedwith *TBX3* gene, coding for another T-box transcriptional

factor. *TBX3* is widely expressed in a variety of tissues including forelimbs and hindlimbs, epithelium of the mammary gland, the genital tubercle and the uterus[31].

DEFECTS IN DORSO-VENTRAL PATTERNING

This disorder category involves nail-patella syndrome, which is autosomal dominant and is expressed with defects affecting the nails, skeleton, kidneys and eyes. Loss of function mutations in the *LMXlB*gene lead to the syndrome[32,33]. *LMXlB* is involved in determination of dorso-ventral patterning of the limb. A mutation of *WIF1* gene has been isolated as potential novel cause of the phenotype[34].

BRACHYDACTYLY

Brachydactyly phenotype may present as an isolated defect or in association with other malformationsand refers to disproportionately short fingers and toes. Isolated brachydactylies usually occur as autosomal dominant traits and show a high degree of phenotypic variability. A locus on chromosome 5p13.3-p13.2 and the Indian hedgehog gene (*IHH*) on chromosome 2q35-36 are involved in A1 brachydacty[35]. A mutation in the human bone morphogenetic protein receptor 1B gene (*BMPR1B*) on chromosome 4q can cause Type A2 brachydactyly. Mutations in *GDF5* alter the receptor binding affinities and can also cause symphalangism. No gene or locus for Type A3 brachydactyly has been identified. B Brachydactyly phenotype involves isolated mutations in the receptor kinase-like orphan receptor 2 gene (*ROR2*) on 9q22[36]. C Brachydactyly phenotype is considered to be caused by mutations in growth/differentiation factor-5 gene (*GDF5*)[37].

SYNDACTYLY

Syndactyly is characterized by the fusion of soft and/or bony tissue of the fingers of the hand and is the most common congenital malformation of the hand in North America and Europe. Syndactyly can occur as an isolated malformation or as part of a syndrome. *HOXD13, FBLN1, GJA1, LMBR1, LRP4, GREM, FGF16*

and and *BHLHA9* genes are incriminated for the disorder, when mutated[38]. Syndactyly type I presents as fusion between the middle and ring fingers. It is an autosomal dominant malformation and the most common type of syndactyly. Mutations in human chromosome 2q34-q36 have been isolated.Syndactyly type II is a dominantly inherited malformation. Its phenotype contains soft tissue syndactyly between the middle and ring fingers and sometimes clinodactyly or camptodactyly of the little finger. *HOXDl3* gene mutations are involved in this disorder[39]. Syndactyly type III affects the ring and little fingers with the little fingers middle phalanx being absent or rudimentary. Mutations in Connexin 43 (*Cx43*) are involved in this type of syndactyly. Syndactyly type IV manifests as syndactyly of all fingers, and syndactyly type V as metacarpal synostosis. The genetic background of the last two types is not yet investigated[40].

CONCLUSION

Genetic hand disorders and their genetic heterogeneity and allelic heterogeneity between families indicate more complex mechanisms besides simple Mendelian inheritance. These mechanisms include underlying genes, epigenetic, and environmental factors[41]. With the advent of NGS technology, including exome sequencing and whole-genome sequencing, new mutations causing hand malformations are isolated and the molecular pathogenesis is exposed. Systematic bioinformatics analysis of the responsible genes, using high-throughput sequencing, is a valuable tool in establishing the precise genotype–phenotype correlations of hand genetic disorders. Diagnosis is still largely postbirth, although prenatal diagnosis *via* molecular and genetic methodologies exists. The expansion of our knowledge related to the mutations leading to different phenotypes, with the use of next generation sequencing analysis, will contribute to prenatal diagnosis, prediction of operative treatment strategy and potential future applications in gene therapy.

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